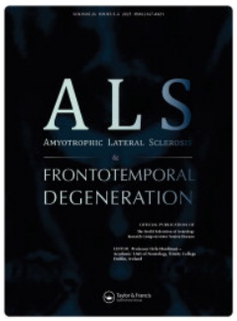

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CASE REPORT

ALSUntangled #80: ISRIB (Integrated stress response InhiBitor)

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Abstract

ALSUntangled reviews alternative and off-label treatments for people living with amyotrophic lateral sclerosis (PALS). Here we assess ISRIB, a molecule that attenuates the integrated stress response (ISR). The ISR is an intracellular signaling network through which cells normally respond to stress, but in ALS it appears to be overactive, leading to the formation of "stress granules" which some but not all investigators believe can triggerapoptotic cell death. ISRIB can attenuate the formation of these stress granules while still allowing parts of protein synthesis to continue. Pre-clinical data demonstrate that ISRIB is beneficial in cell models of ALS. A small number of patients taking ISRIB in Spain report symptomatic improvements with little or no side effects, though we have not been able to independently verify these benefits. There are no clinical trials evaluating ISRIB in any condition and questions about its solubility and bioavailability have arisen. Currently, we do not have enough evidence to endorse the use of ISRIB for treating ALS. We support further research in disease models and clinical trials to study pharmacokinetics, safety and efficacy.

Keywords: *ISRIB, ISR, stress granules*

Introduction

ALSUntangled reviews alternative and off-label treatments (AOTs) voted on by people living with amyotrophic lateral sclerosis (PALS) through our website. Here, we review ISRIB (Integrated Stress Response InhiBitor) for which we have received 2829 requests (1).

ISRIB (2-(4-(2-(5-(3,5-dichlorophenyl)-1,2,4-oxadiazole-3-il) ethyl) phenoxy)-N-isopropyl acetamide), a symmetric bis-glycolamide containing a

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central bi-substituted cyclohexane, is an orally administered agent that inhibits the integrated stress response (ISR) pathway. It first appeared in medical literature in 2013 when it was studied in a mouse model of memory enhancement. ISRIB-treated mice displayed significant improvement in spatial and fear-associated learning (2). Interest of PALS in this compound seems to have increased following publication of an interview with Dr. Peter Walter (the biochemist who discovered ISRIB) in which he describes its benefits in mouse models of traumatic brain injury and neurodegeneration and states "the molecule ISRIB could become a wonder drug" (3). However, at the end of the interview Walter advises against taking ISRIB by patients because "we still don't really know what happens" (3). Following this, ALSUntangled voting for this topic increased dramatically and a group of PALS in Spain began an online spreadsheet to document their experiences with the compound (personal communication from authors JMC, AMB).

Mechanisms

The integrated stress response is a complex intracellular pathway believed to be important in cellular responses to diverse stressors including inflammation, protein misfolding, endoplasmic reticulum dysfunction, viral infection, hypoxia, glucose or amino acid deprivation, and the presence of reactive oxygen species (4). Once activated, it can downregulate protein synthesis and upregulate specific gene expression (4). It also interacts with other pathways including those involving heat shock proteins, autophagy and the unfolded protein response (4). Overactivity of the ISR, which occurs in several ALS pre-clinical models and in PALS (reviewed in 4-6), can lead to the formation of "stress granules" (4–6). Some investigators believe that stress granules are neurotoxic and can trigger protein aggregation and apoptotic cell death (4–6). Others have pointed out that protein aggregation in ALS models can arise independent of stress granules (7,8).

A wide variety of compounds have been utilized to inhibit or attenuate the ISR pathway at various points (reviewed in 4–6). A detailed review of all these compounds is beyond the scope of this article, but it is noteworthy that some are quite toxic (9). IRSIB's mechanism of action differs from more toxic ISR inhibitors in that it blocks enough of the cascade to inhibit the formation of stress granules while still allowing for the synthesis of other important proteins (9–11). As discussed further in the next section, ISRIB treatment in three different familial ALS cell culture models enhances neuronal survival (12–14) and ameliorates aberrant electrophysiology.

Given that ISRIB affects a plausible disease mechanism in ALS cell culture models, we assign a TOE "Mechanisms" grade of B (Table 1).

Pre-clinical models

ISRIB has been studied in three ALS cell models (12–14). In human leukemia cells exposed to a dipeptide repeat protein (a type of protein that is believed to play a role in C9orf72 ALS), pretreatment with ISRIB protected against cell death (12). In rat cortical neurons expressing G93A mSOD1, treatment with ISRIB across a wide range of concentrations (100 nM-100uM) prolonged cell survival (13). Finally, in motor neurons (derived from human pluripotential stem cells) expressing the rare ALS-causing mutation called VAPB P56S, treatment with ISRIB improved some of the abnormal electrophysiology associated with these cells (14). Whether the findings in these cell models can generalize to PALS with genetic or sporadic ALS is currently unknown.

Based on these three studies in ALS cell models, we assign a TOE "Pre-clinical" Grade of B (Table 1).

Of potential interest, treatment with other ISR inhibitors in ALS models has produced more mixed results. In the above-described G93A mSOD1 rat cortical neurons, the ISR inhibitor GSK2606414 failed to prolong survival (13). However, GSK2606414 treatment of rat cortical neurons over-expressing TDP-43 was neuroprotective (15) and mitigated climbing dysfunction in a TDP-43-expressing fly model (15). In G93A mSOD1 mice, treatment with two different ISRIB-like compounds (called 2BAct and PRXS571) resulted in earlier onset denervation and shortened survival (16). It remains unclear whether the differing results in these studies were due to the cell type, the specific ALS pathology induced, or the location targeted within the ISR cascade.

Cases

In Spain, 42 PALS are uploading data about their self-administered ISRIB dosages, side effects and perceived changes in disease progression into an online spreadsheet (personal communication from authors JMC, AMB). No objective measures of ALSFRS-R, gait performance, muscle strength, pulmonary function or safety labs are being routinely uploaded. Subjective improvements have been reported in stamina, general motor performance, sleep, salivation, speech and gait stability.

We did not find any other reports from PALS about their experience with ISRIB.

Based upon the subjective improvements described by PALS in Spain (which have not been

Table 1. Table of evidence grades for ISRIB as an ALS treatment.

	Grade	Explanation
Mechanism	B	Evidence from animal models (but not yet from PALS) suggests that ISR could be involved in ALS pathogenesis, and that inhibiting it could be a useful therapeutic strategy.
Preclinical	B	ISRIB is neuroprotective in cell models of ALS
Cases	D	Subjective reports of symptomatic improvement without validated diagnoses and/or benefits
Trials	U	No published clinical trials of ISRIB in ALS
Risks	U	Unknown. Not systematic description of risks/adverse events

confirmed objectively), we assign a TOE "Cases" grade of D (Table 1).

Clinical trials

Because we found no clinical trials with ISRIB in PALS, we assign a TOE "Trials" grade of U (Table 1).

Of potential interest, two other ISR-targeting compounds have recently been investigated in PALS in the Healey Platform Trial: ABBV-CLS-7262 (fosigotifator, 17) and DNL343 (18). These multicenter trials were randomized, double-blind, placebo-controlled (3:1 active to placebo ratio) and 6-months long. Preliminary analyses suggest that both compounds were safe and well-tolerated but neither slowed ALSFRS-R decline relative to placebo, the trial's main endpoint. An exploratory analysis suggested that decline in muscle strength might be slower at the higher tested dose of ABBV-CLS-7262 relative to placebo (17,18).

Another ISR-targeting compound called guanabenz was tested at three different doses (16 mg, 32 mg and 64 mg daily for 6 months) in a placebo-controlled phase 2 trial (ProMISe) in Italy in 2017 (19). Side-effects were significantly more frequent in guanabenz-treated participants compared to those treated with placebo and trial discontinuation was common in the highest-dose group. Interestingly, bulbar onset patients on 32 or 64 mg daily appeared to benefit in that they were less likely to progress to a higher stage of disease over the duration of the trial compared to those on placebo (19).

Dosing, risks, and costs

The optimal ISRIB dose (if any) or formulation for treating ALS is currently unknown. While ISRIB crosses the blood brain barrier (9) its poor solubility raises about its bioavailability in humans (20,21).

In Spain, ISRIB can be purchased without a prescription (personal communication from authors JMC, AMB). PALS there obtain ISRIB from the PenPeptides Spain website, although it is also sold on many other internet sites (personal communication from authors JMC, AMB). There are two formulations available from PenPeptides: 60 capsules of 10 mg for €106 ($120 and 60 capsules of 30 mg for €199 ($217) (personal communication from authors JMC, AMB). One patient from Spain reportedly sent a sample of ISRIB from PenPeptides to a private laboratory where the presence of the compound was confirmed by mass spectrometry; however, no ISRIB concentration was reported (personal communication from authors JMC, AMB).

As no published human trials using ISRIB were found, we have no information about possible adverse events. Spanish PALS taking the drug have not reported significant side effects other than mild constipation and headache (personal communication from authors JMC, AMB).

We therefore assign a TOE "Risks" grade of U (Table 1).

Conclusion

ISR over-activation may play an important role in ALS pathogenesis, as supported by data from preclinical models and PALS. Several different ISR inhibitors have been tried in ALS models or in PALS with mixed results; but given the different specific actions of these, it is not possible to generalize across the whole class. ISRIB can attenuate parts of the ISR and has shown benefits in cell models of familial ALS. A group of PALS in Spain who are taking ISRIB report subjective improvements in some ALS-related symptoms, but objective evidence is lacking. Reported side effects are minimal, but no published trials of ISRIB exist, leaving questions about safety and tolerability unanswered. In addition, concerns remain about its solubility and human bioavailability. Currently, there is not enough information to support the regular use of ISRIB for treating ALS. Further studies are required to evaluate its pharmacokinetics, safety, and efficacy in PALS.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article

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